REMARKS

Amendments to the Claims

Claims 1-33 are pending. The Applicant respectfully asks the Examiner to replace all prior versions and listings of claims in the present application with the listing of claims currently provided. Claim 1 was amended. The Applicant states that all amended claims do not add new subject matter to the present specification.

Amendment support for Claim 1 regarding "endogenous SNAP-25" can be found throughout the specification at, *e.g.*, ¶¶ 146-146; Fig 8.

Amendment support for Claim 1 regarding "cell-based method" can be found throughout the specification at, *e.g.*, Examples I and II.

Rejection Pursuant to 35 U.S.C. § 102(b) Anticipation

Keller reference

The Examiner has rejected Claims 1, 4, 7, 16, 17, 18, 19, 22,28 and 29 as allegedly being anticipated under 35 U.S.C. § 102(b) over James E. Keller et al., *Persistence of Botulinum Neurotoxin Action in Cultured Spinal Cord Cells*, FEBS Lett. 456(1): 137-142 (1999), hereafter the "Keller reference." The Applicants respectfully ask for reconsideration under 37 C.F.R. § 1.111.

According to *MPEP* § 2131, "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 632 (Fed. Cir. 1987). The Applicants respectfully submit that the Examiner has failed to make a *prima facie* case of anticipation because the Keller reference does not disclose each and every element set forth in the presently claimed method.

The presently claimed method is directed, in part, to a method of detecting BoNT/A activity by contacting a sample to a cell that contains an exogenous FGFR3 wherein said contacted cell is capable of BoNT/A intoxication and detecting the presence of BoNT/A activity of said contacted cell relative to a control cell, where a difference in said BoNT/A activity of said contacted cell as compared to said control cell is indicative of BoNT/A activity. The cell can either transiently or stably contain an exogenous FGFR3. Present specification at ¶ 34. In addition, the cell can be a neuronal or non-neuronal cell "that express low or undetectable levels of endogenous receptor but which have been transfected with, or otherwise engineered to express, one or more exogenous nucleic acid molecules encoding one or more FGFR3s." *Id.* at ¶ 87. The present specification also discloses that the term "Fibroblast Growth Factor 3 Receptor" is synonymous with "FGFR3" and "means a FGFR3 peptide or peptidomimetic which binds BoNT/A in a manner that elicits a BoNT/A intoxication response. FGFR3s useful in the invention encompass, without limitation, wild type FGFR3s, naturally occurring FGFR3 variants, non-naturally FGFR3 variants, such as, e.g., genetically engineered variants produced by random mutagenesis or rational designed, and active fragments derived from a FGFR3s." Present specification at ¶ 36.

The Keller reference discloses a cell-based assay to detect BoNT/A and BoNT/E activity by contacting primary dissociated fetal mouse spinal cord neurons with either BoNT/A or BoNT/E and detecting the presence or absence of SNAP-25 cleavage product by Western blot analysis. *See e.g.*, Keller at p. 138, col. 1, ¶¶ 4-5; p. 138, col. 2, ¶ 3. The Keller reference relied on endogenously expressed FGFR3. *Id.* at abstract, lines 1-3; p. 138, col. 1, ¶ 5. This can also be inferred from the fact that at the time the Keller reference conducted its experiments, the identity of the BoNT/A receptor was unknown. As such, it would have been impossible for the Keller reference to use cells expressing an exogenous FGFR3 because they were not in possession of the required knowledge or an external source of genetic material encoding an FGFR3. As such, the Keller reference does not read on the presently claimed method because it lacks the limitation "exogenous FGFR3." Thus, the Keller reference does not anticipate because it does not set forth each and every element set forth in the presently claimed method. Therefore, the Applicants respectfully request withdrawal of the 35 U.S.C. § 102(b) anticipation rejections against Claims 1, 4, 7, 16, 17, 18, 19, 22, 28 and 29.

The Examiner has taken the position that a naturally occurring FGFR3 contains an exogenous (cell surface) domain and an endogenous (cytoplasmic) domain. Based on this asserted meaning, the Examiner indicates that an endogenous FGFR3 anticipates an exogenous FGFR3 because an endogenous FGFR3 has an exogenous domain. However, the construing of the terms "exogenous" and "endogenous" in such a manner is without any evidentiary basis, and, as such, untenable.

First, the Examiner simply states in a conclusory fashion that "[n]aturally occurring FGFR3 contains both exogenous (cell surface) as well as endogenous domains[.]" The Examiner provided no rationale or reason based on facts how such a tortuous meaning for these two terms was construed. For example, the Examiner has provided no explanation why the terms of art "extracellular" and "intracellular" used to describe whether a protein domain is on the cell surface or is cytoplasmic have been abandoned. In addition, the Examiner has failed to provide any evidence supporting the asserted meaning of the term "exogenous" as defining the cell surface domain of a naturally-occurring FGFR3 or the meaning of the term "endogenous" as defining the cytoplasmic domain of a naturally-occurring FGFR3. Although claim language is to be construed in its broadest terms, the Examiner has not established that this breath included the Examiner's asserted meaning for these terms. Similarly, the Examiner articulated no rationale for such an interpretation, even though, as discussed below, the meaning of the terms "exogenous" and "endogenous" are terms of art that are well known to a person of ordinary skill that plainly excludes the Examiner's asserted meaning.

Second, the enclosed declaration by Dr. Fernandez-Salas indicates that both "exogenous" and "endogenous" are well-known terms of art with precise meanings that clearly rule out the Examiner's asserted meaning for these terms.

In addition, the usage of the terms "exogenous" and "endogenous" in the present application is consistent with the usage described in this declaration. For example, the present specification states that "cells useful in the invention include neuronal and non-neuronal cells that express low or undetectable levels of endogenous receptor but which have been transfected with, or otherwise engineered to express, one or more exogenous nucleic acid molecules encoding one or more FGFR3s." Present specification at ¶ 87. The present specification also discloses various recombinant biology techniques used to introduce

exogenous genes encoding FGFR3 or exogenous FGFR3. *Id.* at ¶¶ 62-64; 73. As another example, Example II describes the identification of FGFR3 containing cell lines by monitoring the cleavage of "endogenously expressed SNAP-25." *Id.* at ¶¶ 145-146. Taken in context, all this statements clarly indicate that "exogenous" and "endogenous" are used as source of origin terms and not geographical location terms as suggested by the Examiner. If one were to accept the Examiner's definition, for example, one would have to conclude that the cells transfected with or otherwise engineered to express exogenous nucleic acid molecules had these molecules located on the cell surface. This is not what a person of ordinary skill in the relevant art would understand "exogenous nucleic acid molecule" to mean.

Furthermore, the status of whether a FGFR3 is a wild-type or naturally-occurring FGFR3 or a non-naturally-occurring FGFR3 is immaterial as both can be an exogenous FGFR3. The terms "exogenous" and "endogenous" are in reference to whether a cell is expressing an FGFR3 naturally from its genome or whether such expression is due to an outside source introduced by genetic manipulation, such as, *e.g.*, transformation or transfection of a plasmid, phagemid, or phage expression vector. For example, if a cell expresses a wild-type FGFR3 gene normally contained in its genome (*i.e.*, present without the need of human manipulation), then this cell has an endogenous FGFR3 because the FGFR3 originated from the expression of genetic material normally present in that cell's genome. However, if a cell does not express a wild-type FGFR3 gene from its genome, then a FGFR3, whether wild-type or non-naturally occurring, must be introduced into the cell using genetic material from an external source. This is an exogenous FGFR3 because this FGFR3 was expressed from a genetic source other than from an FGFR3 gene normally present in that cell's genome. The use of the terms "exogenous" and "endogenous" in the present application is also consistent with this meaning. For example, the present specification discloses that "a neuronal or non-neuronal cell can be transiently or stably engineered to express an exogenous nucleic acid molecule encoding a FGFR3 . . . [or] . . .. a neuronal or non-neuronal cell can be transiently engineered to contain an exogenous FGFR3." Present specification at ¶ 74.

Third, the enclosed declaration by Dr. Fernandez-Salas indicates that the appropriate terms of art used to describe the Examiner's asserted meaning for "exogenous" and "endogenous" are "extracellular" and "intracellular." Furthermore, the usage of "extracellular" and "intracellular" is specifically used in the context a FGFR3 that is outside the cell membrane or a cell surface

receptor that exists at a location that is exogenous to the cell cytoplasm. *See e.g.*, Bernhard Reuss & Oliver von Bohlen und Halbach, *Fibroblast Growth Factors and Their Receptors in the Central Nervous System*, 313(2) Cell Tissue Res. 139-157 (2003), Akio Shimizu et al, *A Novel Alternatively Spliced Fibroblast Growth Factor Receptor 3 Isoform Lacking the Acid Box Domain is Expressed During Chondrogenic Differentiation of ATDC5 Cells*, 276(14) J. Biol. Chem. 11031-11040 (2001), and L-M. Sturla et al., *FGFR3IIIS: A Novel Soluble FGFR3 Spliced Variant That Modulates Growth is Frequently Expressed in Tumour Cells*, 89(7) Br. J. Cancer 1276-1284 (2003). For example, Reuss reviews the prototypic structural hallmarks of FGFRs and describes them as "transmembrane proteins with three extracellular Ig-Like domains (IgI, IgII, and IgIII), an acidic domain between IgI and IgII, a hydropbic transmembrane domain, and an intracellular tyrosine kinase domain." Reuss at p. 141, col. 1, ¶ 3, line 3 to p. 141, col. 2, ¶ 1, line 3. Similarly, Shimizu describes FGFRs as having "three different parts: an extracellular portion with three Ig-like domains, a single transmembrane portion, and a split tyrosine kinase domain inside the cell." Shimizu at p. 11031, col. 2, ¶ 2, lines 1-4. Likewise, Sturla describes the core structure of an FGFR as "an extracellular domain comprising an amino terminal hydrophobic signal peptide followed by three immunoglobulin (Ig)-like loops, a single hydrophobic transmembrane domain sequence and an intracellular split-tyrosine kinase domain." Sturla at p. 1276, col. 1, ¶ 1, lines 5-11. The terms "extracellular" and "intracellular" are used consistently thought out these articles to mean the protein domains that are on the cell surface or cytoplasmic and the use of the terms "exogenous" and "endogenous" in this context are never used.

Thus, the Examiner's use of the terms "exogenous" and "endogenous" is without any evidentiary basis and is contrary to the well-established meaning used in the art and the present specification. Thus, the Keller reference does not anticipate the presently claimed method because it does not set forth the claim element "exogenous FGFR3." Therefore, the Applicants respectfully request withdrawal of the 35 U.S.C. § 102(b) anticipation rejections against Claims 1, 4, 7, 16, 17, 18, 19, 22,28 and 29.

Rejection Pursuant to 35 U.S.C. § 102(e) Anticipation

I. Nebrigic publication

The Examiner has rejected Claims 1 and 4 as allegedly being anticipated under 35 U.S.C. § 102(e) over Dragan Nebrigic, *System and Method For Processing Capacitive Signals*, U.S. Patent Publication 2005/0040907, hereafter the "Nebrigic publication," in light of evidence provided by Foodborne Microbial Pathogens. The Applicants respectfully ask for reconsideration under 37 C.F.R. § 1.111.

The Nebrigic publication discloses microfabricated mechanical resonant sensors and sensor assemblies useful for monitoring a change in force as applied to a surface membrane or a change in the surface properties of the sensor membrane. Nebrigic at ¶ 2. This publication defines "microfabricated" as "the procedures and/or methods, such as bulk and surface micromachining, used to etch, deposit, pattern, dope, form and/or fabricate structures using substrates such as silicon and the like." *Id.* at ¶ 27. The Nebrigic publication defines "sensor" as "an apparatus or device that can respond to an external stimulus such as, a change in mass on a surface, pressure, force, or a particular motion, where the apparatus can transmit a resulting signal to be measured and/or detected." *Id.* at ¶ 16. This publication discloses that the surface membrane of the sensor is fabricated "from an electrically conductive material, such as doped single crystal silicon, doped polysilicon, metal or any composite thereof . . . [or from] non-conductive materials such as silicon nitride, silicon dioxide, phosphosilicate glass, borophosphosilicate glass." *Id.* at ¶ 38. As such, the Nebrigic publication discloses a mechanical device useful for detecting an electrical signal.

The Nebrigic publication does not read on the presently claimed method because it discloses a "mechanical-based" devices and methods for using such "mechanical-based" devices, and not a "cell-based" method as presently claimed. Additionally, the Nebrigic publication detects activity by changes in an electrical signal and not by the presence of a cleavage product of a specific protein. Thus, the Nebrigic publication does not anticipate because it does not set forth each and every element set forth in the presently claimed method. Therefore, the Applicants respectfully request withdrawal of the 35 U.S.C. § 102(e) anticipation rejections against Claim 1, and 4.

II. Steward patent

The Examiner has rejected Claims 1, 18, and 28-33 as allegedly being anticipated under 35 U.S.C. § 102(e) over Lance E. Steward et al., *FRET Protease Assays For Botulinum Serotype A/E Toxins*, U.S. Patent 7,208,285, hereafter the "Steward patent." The Applicants respectfully ask for reconsideration under 37 C.F.R. § 1.111.

The Steward patent discloses a method of determining BoNT/A activity by treating a FRET-based SNAP-25 substrate with BoNT/A, exciting the sample with a wavelength, and determining a difference in resonance transfer energy of the treated sample relative to a control sample. *See e.g.*, abstract col. 1, line 63 through col. 2, line 7; Claim 1. The FRET-based SNAP-25 substrate is an exogenous substrate because it can only be produced recombinantly using molecular genetic techniques. See e.g., Example I. Clostridial toxin activity is detected solely by the difference in resonance transfer energy due to the cleavage, or lack thereof, of this exogenous FRET-based SNAP-25 substrate.

The Steward patent does not read on the presently claimed method because it discloses a method of determining BoNT/A activity that relies on the cleavage of an exogenous FRET-based SNAP-25 substrate to detect BoNT/A activity, and not the cleavage of an endogenous SNAP-25 as presently claimed. Thus, the Steward patent does not anticipate because it does not set forth each and every element set forth in the presently claimed method. Therefore, the Applicants respectfully request withdrawal of the 35 U.S.C. § 102(e) anticipation rejections against Claims 1, 18, and 28-33.

III. Fernandez-Salas patent

The Examiner has rejected Claims 1, 4-8, 16-22, and 28-33 as allegedly being anticipated under 35 U.S.C. § 102(e) over Ester Fernandez-Salas et al., *Cell-Based Fluorescence Resonance Energy Transfer (FRET) Assays For Clostridial Toxins*, U.S. Patent 7,183,066, hereafter the "Fernandez-Salas patent." The Applicants respectfully ask for reconsideration under 37 C.F.R. § 1.111.

The Fernandez-Salas patent discloses a method of determining Clostridial toxin activity by contacting a cell containing at least one receptor for a Clostridial toxin and a FRET-based substrate, exciting the cell with a wavelength, and determining a difference in resonance transfer energy of the treated sample relative to a control sample. *See e.g.*, abstract, Claim 1. The FRET-based substrate is an exogenous substrate because it can only be produced recombinantly using molecular genetic techniques. This recombinantly produced substrate is then introduced into the cell by routine methods. Clostridial toxin activity is detected solely by the difference in resonance transfer energy due to the cleavage, or lack thereof, of this exogenous FRET-based SNAP-25 substrate.

The Fernandez-Salas patent does not read on the presently claimed method because it discloses a method of determining BoNT/A activity that relies on the cleavage of an exogenous FRET-based SNAP-25 substrate to detect BoNT/A activity, and not the cleavage of an endogenous SNAP-25 as presently claimed. Thus, the Fernandez-Salas patent does not anticipate because it does not set forth each and every element set forth in the presently claimed method. Therefore, the Applicants respectfully request withdrawal of the 35 U.S.C. § 102(e) anticipation rejections against Claims 1, 4-8, 16-22, and 28-33.

Rejection Pursuant to Judicially-Created Obvious-Type Double Patenting

U.S. Patent 7,183,066.

The Examiner has rejected Claims 1, 4-8, 16-22, and 28-33 as allegedly being unpatentable over allowed Claims 1, 4-9, 28-32 and 39 U.S. Patent No. 7,183,066, Ester Fernandez-Salas et al., *Cell-Based Fluorescence Resonance Energy Transfer (FRET) Assays For Clostridial Toxins*, under the judicially created doctrine of obviousness-type double patenting. The Applicants respectfully ask for reconsideration under 37 C.F.R. § 1.111.

According to *MPEP* § 804, obviousness-type double patenting requires rejection of a second "to issue" application claim when the claimed subject matter is not patentably distinct from the subject matter claimed in a commonly owned first "to issue" patent. Two inventions are distinct from one another "if the inventions as claimed are not connected in at least one of design, operation, or effect (*e.g.*, can be made by, or used in, a materially different process)."

MPEP § 802.01. The "analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. § 103 obviousness determination." *MPEP* § 800. However, according to *MPEP* § 804.03, an obvious-type double patenting rejection is not made over the disclosure of the first "to issue" patent, but rather is based solely on the precise invention claimed thereof. See, *e.g.*, *In re Vogel*, 422 F.2d 438, 441 (C.C.P.A. 1970). As such, the claim of the second "to issue" application must be the same or an obvious variant of a claim to the first "to issue" patent. All aspects of the claims must be considered and not just a single feature of the claim. *MPEP* § 804.

The Applicants respectfully submit that a prima facie case for obviousness-type double patenting cannot be maintained over the presently amended Claim Set. The presently claimed cell-based method of determining BoNT/A activity is directed, in part, to treating a cell containing an endogenous SNAP-25 and determining the presence of endogenous SNAP-25 cleavage product in the treated cell.

The Fernandez-Salas patent claims, in part, a method of determining Clostridial toxin activity by treating a cell containing a FRET-based SNAP-25 substrate, exciting the cell with a wavelength, and determining a difference in resonance transfer energy of the treated cell relative to a control cell. *See e.g.*, abstract, Claim 1. As discussed above, the FRET-based substrate is an exogenous substrate that is introduced into the cell by routine methods. Clostridial toxin activity is detected solely by the difference in resonance transfer energy due to the cleavage, or lack thereof, of this exogenous FRET-based SNAP-25 substrate.

As such, the presently claimed method is not obvious to the claimed method of the Fernandez-Salas patent because 1) by definition, an endogenous SNAP-25 is not a FRET-based SNAP-25 substrate since an endogenous SNAP-25 cannot comprise the modifications required to make a FRET-based substrate, *e.g.*, a donor fluorophore, an acceptor fluorophore; and 2) by definition, an endogenous SNAP-25 cannot be an exogenous substrate since an endogenous SNAP-25 is expressed form the genome of the cell whereas a FRET-based SNAP-25 substrate must be introduced into a cell using recombinant biology techniques.

Furthermore, modifying the FRET-based SNAP-25 substrate to an endogenous SNAP-25 as presently claimed would destroy the claimed method of the Fernandez-Salas patent for its

intended purpose. According to MPEP §2143.01, if proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. In this case, modifying the method claimed in the Fernandez-Salas patent to use an endogenous SNAP-25 as presently claimed would make it inoperable because an endogenous SNAP-25 as presently claimed cannot function as a FRET-based SNAP-25 substrate since an endogenous SNAP-25 lacks donor and acceptor fluorophores. As such, the claimed method of the Fernandez-Salas patent would not detect BoNT/A activity because there would be no FRET-based SNAP-25 substrate to excite and no resonance transfer energy to detect.

In addition, modifying the FRET-based SNAP-25 substrate to an endogenous SNAP-25 as presently claimed would change the principle of operation of the method claimed in the Fernandez-Salas patent. According to *MPEP* § 2143.01, "if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious." As such, a proposed modification cannot substantially reconstruct and redesign the elements of the invention disclosed in the primary reference or a change in the basic principle under which the invention claimed in the primary reference was designed to operate. *Id.* In this case, modifying the method claimed in the Fernandez-Salas patent to use an endogenous SNAP-25 as presently claimed would change its principle of operation because detection would be based on a principle other that resonance energy transfer. However, the endogenous SNAP-25 is unable to be excited by a wavelength and is unable to transfer resonance energy, and as such, Clostridial toxin activity could not be determined. Thus, the principle of operation of the method claimed in the Fernandez-Salas patent would change.

Thus, the Applicants respectfully submit that the method claimed in the Fernandez-Salas patent does not make the presently claimed method obvious because 1) the endogenous SNAP-25 presently claimed is not an exogenous, FRET-based SNAP-25 substrate; 2) substitution of the endogenous SNAP-25 presently claimed would destroy the claimed method of the Fernandez-Salas patent for its intended purpose; and 3) substitution of the endogenous SNAP-25 presently claimed would change the principle of operation of the method claimed in

the Fernandez-Salas patent. Therefore, the Applicants respectfully request withdrawal of the obviousness-type double patenting rejection against Claims 1, 4-8, 16-22, and 28-33.

U.S. Patent 7,208,285.

The Examiner has rejected Claims 1, 18, and 28-33 as allegedly being unpatentable over allowed Claims 1, 4-8, 27, 29, 31-35, 50, 58, 66, 67, 69-77 and 84 U.S. Patent No. 7,208,285, Lance E. Steward et al., *FRET Protease Assays For Botulinum Serotype A/E Toxins*, under the judicially created doctrine of obviousness-type double patenting. The Applicants respectfully ask for reconsideration under 37 C.F.R. § 1.111.

The Applicants respectfully submit that a prima facie case for obviousness-type double patenting cannot be maintained over the presently amended Claim Set. As discussed above, the presently claimed cell-based method of determining BoNT/A activity is directed, in part, to treating a cell containing an endogenous SNAP-25 and determining the presence of endogenous SNAP-25 cleavage product in the treated cell.

The Steward patent claims, in part, a method of determining BoNT/A activity by treating a FRET-based SNAP-25 substrate, exciting the FRET-based substrate with a wavelength, and determining a difference in resonance transfer energy of the treated sample relative to a control sample. *See e.g.*, abstract, Claim 1. Like the FRET-based substrate disclosed in the Fernandez-Salas patent, the FRET-based substrate of the Steward patent is an exogenous, recombinantly produced substrate. Clostridial toxin activity is detected solely by the difference in resonance transfer energy due to the cleavage, or lack thereof, of this exogenous FRET-based SNAP-25 substrate.

The same pointed discussed above for the obvious-type double patenting regarding the claimed method of the Fernandez-Salas patent are applicable to the claimed method of the Steward patent. Thus, modifying the method claimed in the Steward patent to use an endogenous SNAP-25 as presently claimed would make it inoperable because an endogenous SNAP-25 as presently claimed cannot function as a FRET-based SNAP-25 substrate. As such, an endogenous SNAP-25 is neither 1) a FRET-based SNAP-25 substrate since an endogenous SNAP-25 cannot comprise the modifications required to make a FRET-

based substrate, *e.g.*, a donor fluorophore, an acceptor fluorophore; nor 2) an exogenous substrate since an endogenous SNAP-25 is expressed form the genome of the cell whereas a FRET-based SNAP-25 substrate must be introduced into a cell using recombinant biology techniques. In addition, the claimed method of the Steward patent would not detect BoNT/A activity because there would be no FRET-based SNAP-25 substrate to excite and no resonance transfer energy to detect. Lastly, modifying the method claimed in the Steward patent to use an endogenous SNAP-25 as presently claimed would change its principle of operation because detection would be based on a principle other that resonance transfer energy. However, the endogenous SNAP-25 is unable to be excited by a wavelength and is unable to transfer resonance energy, and as such, Clostridial toxin activity could not be determined. Thus, the principle of operation of the method claimed in the Steward patent would change.

Thus, as discussed above, the Applicants respectfully submit that the method claimed in the Steward patent does not make the presently claimed method obvious because 1) the endogenous SNAP-25 presently claimed is not an exogenous, FRET-based SNAP-25 substrate; 2) substitution of the endogenous SNAP-25 presently claimed would destroy the claimed method of the Steward patent for its intended purpose; and 3) substitution of the endogenous SNAP-25 presently claimed would change the principle of operation of the method claimed in the Steward patent. Therefore, the Applicants respectfully request withdrawal of the obviousness-type double patenting rejection against Claims 1, 18, and 28-33.

Restriction Requirement pursuant to 35 U.S.C. §121

The Applicants' respectfully request that Claims 2 and 3 be reinstated and examined on the ground that the Examiner misconstrued the established meanings of "exogenous" and "endogenous" as well as the well-known meanings of "transiently contained FGFR3" and "stably contained FGFR3." The Applicants respectfully ask for reconsideration under 37 C.F.R. § 1.111.

The species election against Claims 2 and 3 is respectfully traversed. Claims 2 and 3 are directed towards whether an exogenous FGFR3 that is transiently or stably contained within

the cell. The Examiner's reasoning discussed in the September 22, 2008 Office Action at p. 3 is equally applicable to Claim 1 because the exogenous FGFR3 of Claim 1 can either be transiently expressed or stably expressed. As such, Claims 2 and 3 only limit claim 1 and do not introduce an inventive concept not already encompassed by Claim 1.

The Examiner's construed meaning of the terms "transiently containing" and "stably containing" to refer to the length of time that an FGFR3 is present on the cell surface as opposed to contained within the cytoplasm is contrary to the meaning given to these terms in the present specification. For example, the present specification defines "transiently containing" as "a FGFR3 that is temporarily introduced into a cell in order to perform the assays disclosed in the present specification." Present specification at ¶ 56. The present specification further elaborates this meaning by indicating that a cell transiently containing a FGFR3 disclosed in the specification may include a cell that contains a FGFR3 for, e.g., at most about one day to at most about ten days. *Id.* Likewise, the present specification defines "stably containing" as "a FGFR3 that is introduced into a cell and maintained for long periods of time in order to perform the assays of the present specification. Stably-maintained nucleic acid molecules encompass stably-maintained nucleic acid molecules that are extra-chromosomal and replicate autonomously and stably-maintained nucleic acid molecules that are integrated into the chromosomal material of the cell and replicate non-autonomously." *Id.* at 58. The present specification further elaborates this meaning by indicating that a cell stably containing a FGFR3 disclosed in the specification may include a cell that contains a FGFR3 for, e.g., at least ten days to at least 500 days. *Id.*

Furthermore, the Applicants reiterate that this aspect of the Group I invention does not represent a different general inventive concept because both claims are still within the same inventive concept of detecting BoNT/A activity and do not represent a mammalian FGFR3 different from that of Claim 1. Thus, the Applicants respectfully request rejoinder of Claims 2 and 3.

CONCLUSION

For the above reasons the Applicant respectfully submits that the claims are in condition for allowance, and the Applicant respectfully urges the Examiner to issue a Notice to that effect. Should there be any questions, the Examiner is invited to call the undersigned agent. Please use Deposit Account 01-0885 for the payment of any extension of time fees pursuant to 37 C.F.R. § 1.136 or any other fees due in connection with the current response.

Respectfully submitted,

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